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INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)



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(51) Internationale Patentklassifikation 6 : C07D		A2	(11) Internationale Veröffentlichungsnummer: WO 98/16507 (43) Internationales Veröffentlichungsdatum: 23. April 1998 (23.04.98)
(21) Internationales Aktenzeichen: PCT/EP97/05432		Am Tescher Busch 13, D-42327 Wuppertal (DE). HÜTTER, Joachim [DE/DE]; Teschensudberger Strasse 13, D-42349 Wuppertal (DE). DEMBOWSKY, Klaus [DE/DE]; Bismarckstrasse 85, D-42115 Wuppertal (DE). ARLT, Dieter [DE/DE]; Papenhauser Strasse 10, D-32657 Lemgo (DE).	
(22) Internationales Anmeldedatum: 2. Oktober 1997 (02.10.97)		(74) Gemeinsamer Vertreter: BAYER AKTIENGESELLSCHAFT ; D-51368 Leverkusen (DE).	
(30) Prioritätsdaten: 196 42 319.8 14. Oktober 1996 (14.10.96) DE 196 42 320.1 14. Oktober 1996 (14.10.96) DE 196 42 322.8 14. Oktober 1996 (14.10.96) DE 196 42 323.6 14. Oktober 1996 (14.10.96) DE		(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
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(54) Title: NEW HETEROCYCLYL METHYL-SUBSTITUTED PYRAZOL DERIVATES			
(54) Bezeichnung: NEUE HETEROCYCLYL METHYL-SUBSTITUIERTE PYRAZOLDERIVATE			
(57) Abstract			
Disclosed are new heterocyclmethyl-substituted pyrazol derivates, the preparation thereof and their use as drug products, particularly for treating cardiovascular diseases.			
(57) Zusammenfassung			
Die vorliegende Erfindung betrifft neue Heterocyclmethyl-substituierte Pyrazolderivate, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als Arzneimittel zur Behandlung von Herz-Kreislauf-Erkrankungen.			
6166027 Le 17 32080 US patents 6387940 SNS 644,305 645,834 648,082			



US006166027A

United States Patent [19]

Straub et al.

[11] Patent Number: **6,166,027**
[45] Date of Patent: **Dec. 26, 2000**

[54] **HETEROCYCLYL METHYL-SUBSTITUTED PYRAZOLE DERIVATIVES AND THEIR USE FOR TREATING CARDIOVASCULAR DISEASES**

[75] Inventors: Alexander Straub, Wuppertal; Chantal Fürstner, Mülheim/Ruhr; Ulrich Niewöhner, Wermelskirchen; Thomas Jaetsch, Köln; Achim Feurer, Odenthal; Raimund Kast, Wuppertal; Johannes-Peter Stasch, Solingen; Elisabeth Perzborn; Joachim Hütter, both of Wuppertal; Klaus Dembowsky, Schriesheim; Dieter Arlt, Lemgo, all of Germany

[73] Assignee: **Bayer Aktiengesellschaft, Leverkusen, Germany**

[21] Appl. No.: **09/284,172**

[22] PCT Filed: **Oct. 2, 1997**

[86] PCT No.: **PCT/EP97/05432**

§ 371 Date: **Apr. 9, 1999**

§ 102(e) Date: **Apr. 9, 1999**

[87] PCT Pub. No.: **WO98/16507**

PCT Pub. Date: **Apr. 23, 1998**

[30] **Foreign Application Priority Data**

Oct. 14, 1996 [DE] Germany 196 42 319
Oct. 14, 1996 [DE] Germany 196 42 320
Oct. 14, 1996 [DE] Germany 196 42 322
Oct. 14, 1996 [DE] Germany 196 42 323

[51] Int. Cl.⁷ A61K 31/506; A61P 9/00

[52] U.S. Cl. 514/269; 544/238; 544/295; 544/328; 544/333; 544/405

[58] **Field of Search** 546/275.7; 544/333; 514/269

[56] **References Cited**

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Primary Examiner—Robert W. Ramsuer
Attorney, Agent, or Firm—Norris, McLaughlin & Marcus, P.A.

[57]

ABSTRACT

The present invention relates to new heterocyclylmethyl-substituted pyrazole derivatives, processes for their preparation and their use as medicaments, in particular as medicaments for treatment of cardiovascular diseases.

14 Claims, No Drawings

TABLE IV/5-continued

Ex. No. Structure	Yield/ melting point	R_f
IV/203 	45% 158° C.	0.14 (H:EE 1:1)

*EE = ethyl acetate
H = hexane
P = petroleum ether
T = toluene

What is claimed is:

1. A 1-Heterocycl-methyl-substituted pyrazole of the 25 formula (II-I)



in which

R²⁰ represents a 6-membered aromatic heterocyclic ring having up to 3 nitrogen atoms, which is optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, mercaptyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano, azido, halogen, phenyl and/or a group of the formula

$-NR^{23}R^{24}$

wherein

R²³ and R²⁴ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, hydroxyl, amino or by straight-chain or branched alkoxy, acyl or alkoxycarbonyl having in each case up to 5 carbon atoms,

or

R²³ and R²⁴, together with the nitrogen atom, form a 3- to 60 7-membered saturated or partly unsaturated heterocyclic ring, which can optionally additionally contain an oxygen or sulphur atom or a radical of the formula $-NR^{25}$,

wherein

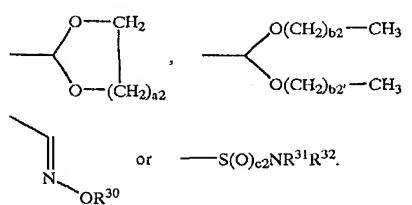
R²⁵ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

and/or is substituted by straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, amino, halo carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino having in each case up to 5 carbon atoms or by a radical of the formula $-OR^{26}$,

wherein R²⁶ denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula $-SiR^{27}R^{28}R^{29}$,

wherein R²⁷, R²⁸ and R²⁹ are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

and/or is optionally substituted by a radical of the formula



wherein

b2 and b2' are identical or different and denote the number 0, 1, 2 or 3,

a2 denotes the number 1, 2 or 3,

R³⁰ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

c2 denotes the number 1 or 2 and

R³¹ and R³² are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms or by aryl having 6 to 10 carbon atoms, which in its turn can be substituted by halogen, or

denote aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, or

denote cycloalkyl having 3 to 7 carbon atoms, or

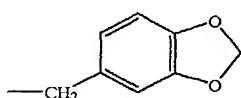
R³¹ and R³², together with the nitrogen atom, form a 5- to 7-membered saturated heterocyclic ring, which

161

can optionally contain a further oxygen atom or a radical $-\text{NR}^{33}$,

wherein

R^{33} denotes hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a radical of the formula



or denotes benzyl or phenyl, wherein the ring systems are optionally substituted by halogen,

R^{21} and R^{22} , including the double bond, form a 5-membered aromatic heterocyclic ring having a heteroatom from the series consisting of S, N and/or O, or a phenyl ring, which are optionally substituted up to 3 times in an identical or different manner by formyl, 25 mercaptyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkylthio, alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms, nitro, cyano, azido, halogen, phenyl or straight-chain or branched 30 alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 5 carbon atoms, or are optionally 35 substituted by a group of the formula $-\text{S}(\text{O})_{c2}\text{NR}^{31}\text{R}^{32}$ wherein c_2 , R^{31} and R^{32} have the abovementioned meaning of c_2 , R^{31} and R^{32} and are identical to or different from these,

A^2 represents phenyl or a 5- to 6-membered aromatic or saturated heterocyclic ring having up to 3 heteroatoms from the series consisting of S, N and/or O, which is optionally substituted up to 3 times in an identical or 45 different manner by mercaptyl, hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacetyl, alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms, nitro, cyano, trifluoromethyl, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, 50 carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 5 carbon atoms,

and/or is substituted by a group of the formula $-(\text{CO})_{a2}\text{NR}^{34}\text{R}^{35}$,

wherein

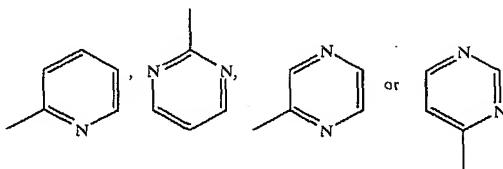
a_2 denotes the number 0 or 1,

R^{34} and R^{35} are identical or different and denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl having in each case up to 5 carbon atoms, and an isomer, salt and N-oxide thereof.

162

2. A compound according to claim 1 of the formula (II-I), in which

R^{20} represents a radical of the formula

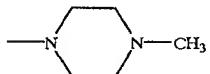


15 which are optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl and/or a group of the formula

$-\text{NR}^{23}\text{R}^{24}$,

wherein

R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched acyl having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, amino or by straight-chain or branched alkoxy having up to 3 carbon atoms, or R^{23} and R^{24} , together with the nitrogen atom, form a morpholine ring or a radical of the formula

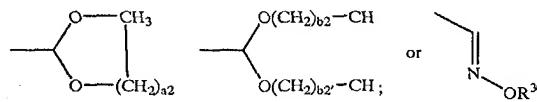


and/or are substituted by straight-chain or branched alkyl having up to 5 carbon atoms, which in its turn can be 40 substituted by hydroxyl, amino, fluo carboxyl, straight-chain or branched acyl, alkoxy, alkoxy carbonyl or acylamino having in each case up to 4 carbon atoms or by a radical of the formula $-\text{OR}^{26}$,

wherein

R^{26} denotes straight-chain or branched acyl having up to 4 carbon atoms,

and/or are optionally substituted by a radical of the formula



wherein

b_2 and b_2' are identical or different and denote the number 0, 1, 2 or 3,

a_2 denotes the number 1, 2 or 3,

R^{30} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^{21} and R^{22} , including the double bond, form a furyl, thiienyl or phenyl ring, which are optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in

each case up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms,

A^2 represents phenyl, or represents tetrahydropyranyl, furyl, tetrahydrofuryl, morpholinyl, pyrimidyl, pyridazinyl or pyridyl, which are optionally substituted up to twice in an identical or different manner by hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacetyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms,

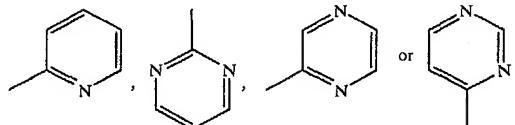
and/or are substituted by a group of the formula $-(CO)_{d2}-NR^{34}R^{35}$ wherein

$d2$ denotes the number 0 or 1,

R^{34} and R^{35} are identical or different and denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl having in each case up to 4 carbon atoms, and an isomer, salt and N-oxide thereof.

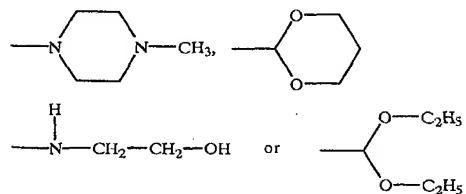
3. A compound according to claim 1 of the formula (II-I), in which

R^{20} represents a radical of the formula



wherein the ring systems are optionally substituted up to 3 times in an identical or different manner by formyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms, methylamino, amino, fluorine, chlorine, bromine, cyano, azido or straight-chain or branched alkyl having up to 4 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, amino, straight-chain or branched acyl, alkoxy, alkoxy carbonyl or acylamino having in each case up to 3 carbon atoms,

and/or are optionally substituted by a radical of the formula



R^{21} and R^{22} , including the double bond, form a furyl, thienyl or phenyl ring, which are optionally substituted up to twice in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in

each case up to 4 carbon atoms, nitro, cyano, fluorine, chlorine, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms,

A^2 represents phenyl, tetrahydropyranyl, tetrahydrofuryl, furyl or pyridyl, which are optionally substituted up to twice in an identical or different manner by formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacetyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or represents straight-chain or branched alkyl having up to 3 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms, and/or are substituted by a group of the formula $-(CO)_{d2}-NR^{34}R^{35}$,

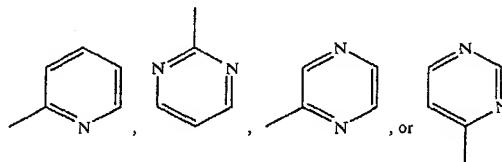
wherein

$d2$ denotes the number 0 or 1,

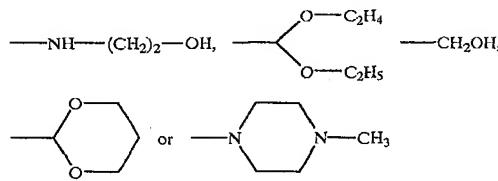
R^{34} and R^{35} are identical or different and denote hydrogen or straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, and an isomer, salt and N-oxide thereof.

4. A compound according to claim 1 of the formula (II-I), in which

R^{20} represents a radical of the formula



wherein the abovementioned heterocyclic ring systems are optionally substituted up to 3 times in an identical or different manner by methyl, fluorine, formyl, amino, cyano, methoxy, methoxycarbonyl, methylamino, chlorine or by a radical of the formula



R^{21} and R^{22} , including the double bond, together form a phenyl ring and

A^2 represents phenyl, which is optionally substituted by fluorine or cyano, and an isomer, salt and N-oxide thereof.

5. A pharmaceutical composition comprising at least one compound of the formula (II-I) according to claim 1.

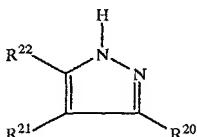
6. A pharmaceutical composition comprising at least one compound of the formula (II-I) according to claim 1 and at least one organic nitrate or an NO donor.

7. A pharmaceutical composition comprising at least one compound of the general formula (II-I) according to claim 1 and compounds which inhibit the breakdown of cyclic guanosine monophosphate (cGMP).

165

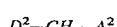
8. A process for preparing a compound of the formula (II-I) according to claim 1, comprising:

A) reacting compounds of the formula (II-II)



in which

R²⁰, R²¹ and R²² are defined as in claim 1, with compounds of the formula (II-III)



in which

A² is defined as in claim 1,

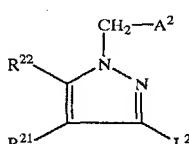
and

D² represents triflate or halogen,

in an inert solvent and, optionally in the presence of a base,

or

B) reacting compounds of the formula (II-IV)



in which

A², R²¹ and R²² are defined as in claim 1

and

L² represents a radical of the formula —SnR³⁶R³⁷R²⁸,

ZnR³⁹,

iodine or triflate

wherein

R³⁶, R³⁷ and R³⁸ independently denote straight-chain or branched alkyl having up to 4 carbon atoms

and

R³⁹ denotes hydrogen with compounds of the formula (II-V)



166

in which

R²⁰ is defined as in claim 1

and

in the case where L²=SnR³⁶R³⁷R³⁸ or ZnR³⁹

T² represents triflate or halogen,

and

in the case where L²=iodine or triflate,

T² represents a radical of the formula S³⁶R³⁷R³⁸,

ZnR³⁹ or BR⁴⁰R⁴¹,

wherein

R³⁶, R³⁷, R³⁸ and R³⁹ have the above mentioned meanings

and

R⁴⁰ and R⁴¹ independently denote hydroxyl aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring,

in a palladium-catalysed reaction in an inert solvent.

9. The process according to claim 8, which is for the preparation of a compound of formula (II-I) which contains a radical —S(O)_{c2}.NR³¹R³² or —S(O)_{cd}.NR³¹R³², said process further comprising reacting an unsubstituted compound of formula (II-I) with thionyl chloride to produce an intermediate product, and thereafter reacting said intermediate product with HNR³¹R³² or HNR³¹R³².

10. The process according to claim 8, which further comprises introducing or varying R²⁰, R²¹, R²² and/or A² by customary methods, preferably by reduction, oxidation, splitting off of protective groups and/or nucleophilic substitution.

11. The process according to claim 8 wherein, D² represents bromine or T² represents bromine.

12. Method for the treatment of cardiovascular diseases, said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (II-I) according to claim 1.

13. Method for preventing or treating the consequences of a cerebral infarction event said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (II-I) according to claim 1.

14. The method according to claim 13, wherein the cerebral infarction event is an apoplexia cerebri selected from the group consisting of apoplexy, cerebral ischaemias and crania-cerebral trauma.

50

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,166,027
DATED : December 26, 2000
INVENTOR(S) : Straub et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 166.

Line 10, delete "BR⁴⁰R⁴⁰," and substitute -- BR⁴⁰R⁴¹, --
Line 28, delete "HNR³¹R³²," and substitute -- HNR³¹R³², --

Signed and Sealed this

Twenty-sixth Day of February, 2002

Attest:

Attesting Officer



JAMES E. ROGAN
Director of the United States Patent and Trademark Office



US006387940B1

(12) **United States Patent**
Straub et al.

(10) **Patent No.:** US 6,387,940 B1
(45) **Date of Patent:** May 14, 2002

(54) **HETEROCYCLYL METHYL-SUBSTITUTED PYRAZOLE DERIVATIVES**

(75) **Inventors:** Alexander Straub, Wuppertal; Chantal Fürstner, Mülheim/Ruhr; Ulrich Niewöhner, Wermelskirchen; Thomas Jaetsch, Köln; Achim Feurer, Odenthal; Raimund Kast, Wuppertal; Johannes-Peter Stasch, Solingen; Elisabeth Perzborn; Joachim Hütter, both of Wuppertal; Klaus Dembowsky, Schriesheim; Dieter Arlt, Lemgo, all of (DE)

(73) **Assignee:** Bayer Aktiengesellschaft, Leverkusen (DE)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 8 days.

(21) **Appl. No.:** 09/644,179

(22) **Filed:** Aug. 23, 2000

Related U.S. Application Data

(62) **Division of application No. 09/284,172, filed as application No. PCT/EP97/05432 on Oct. 2, 1997, now Pat. No. 6,166,027.**

(30) **Foreign Application Priority Data**

Oct. 14, 1996 (DE) 196 42 320
Oct. 14, 1996 (DE) 196 42 323
Oct. 14, 1996 (DE) 196 42 322
Oct. 14, 1996 (DE) 196 42 319

(51) **Int. Cl.⁷** A61K 31/4155; A61P 9/12; C07D 407/04

(52) **U.S. Cl.** 514/403; 546/275.7; 548/235; 548/236; 548/181; 548/311.7; 548/361.1

(58) **Field of Search** 548/361.1, 235; 514/403

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S.-M. Yu et al., "Inhibition of Platelet . . . Vivo", vol. 87, No. 9, May 1, 1996, pp. 3758-3767.

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C.R. Self, et al., "Romazarit: A Potential Disease . . . Drug" Journal of Medicinal Chemistry, vol. 34, No. 2, 1991, Washington, U.S. pp. 772-777.

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Primary Examiner—Robert W. Ramsuer

(74) **Attorney, Agent, or Firm:** Norris McLaughlin & Marcus

ABSTRACT

The present invention relates to new heterocyclylmethyl-substituted pyrazole derivatives, processes for their preparation and their use as medicaments, in particular as medicaments for treatment of cardiovascular diseases.

15 Claims, No Drawings

TABLE IV/5-continued

Ex. No.	Structure	Yield/ melting point R _f
IV/201		89% 131° C. (H:EE 1:1) 0.61
IV/202		76% 152° C. (H:EE 1:1) 0.39
IV/203		45% 158° C. (H:EE 1:1) 0.14

*EE = ethyl acetate

H = hexane

P = petroleum ether

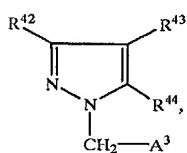
T = toluene

What is claimed is:

1. A 3-Heterocyclyl-substituted pyrazole derivative of the formula (III-I)

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(III-I)



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optionally substituted up to 3 times in an identical or different manner by formyl, phenyl, mercaptyl, carboxyl, trifluoromethyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxy carbonyl having in each case up to 6 carbon atoms, nitro, cyano, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, halogen, trifluoromethyl, amino, carboxyl, straight-chain or branched acyl, alkoxy, alkoxy carbonyl or acylamino having in each case up to 5 carbon atoms or by a radical of the formula —OR⁴⁵, wherein

R⁴⁵ denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula —SIR⁴⁶R⁴⁷R⁴⁸, wherein

R⁴⁶, R⁴⁷ and R⁴⁸ are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

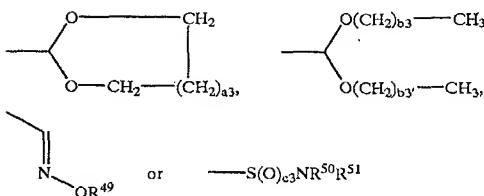
in which

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R⁴² represents a saturated 6-membered heterocyclic ring having up to 2 heteroatoms from the series consisting of S, N and/or O or represents a 5-membered aromatic or saturated heterocyclic ring having 2 to 3 heteroatoms from the series consisting of S, N and/or O, which can also be bonded via a nitrogen atom and which are

163

and/or can be substituted by a radical of the formula



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wherein

a3, b3 and b3' denote the number 0, 1, 2 or 3,
R⁴⁹ denotes hydrogen or straight-chain or branched
alkyl having up to 4 carbon atoms,

c3 denotes the number 1 or 2 and

R⁵⁰ and R⁵¹ are identical or different and denote
hydrogen or straight-chain or branched alkyl having
up to 10 carbon atoms, which is optionally
substituted by cycloalkyl having 3 to 8 carbon
atoms or by aryl having 6 to 10 carbon atoms,
which in its turn can be substituted by halogen, or
denote aryl having 6 to 10 carbon atoms, which is
optionally substituted by halogen, or

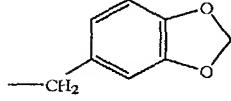
denote cycloalkyl having 3 to 7 carbon atoms, or
R⁵⁰ and R⁵¹, together with the nitrogen atom, form

a 5- to 7-membered saturated heterocyclic ring,

which can optionally contain a further oxygen
atom or a radical —NR⁵², wherein

R⁵² denotes hydrogen, straight-chain or branched
alkyl having up to 4 carbon atoms or a radical

of the formula



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or denotes benzyl or phenyl, wherein the ring
systems are optionally substituted by halogen,
R⁴³ and R⁴⁴, including the double bond, form a
5-membered aromatic heterocyclic ring having one
heteroatom from the series consisting of N, S and/or O,
or a phenyl ring, which are optionally substituted up to
3 times in an identical or different manner by formyl,
carboxyl, hydroxyl, amino, straight-chain or branched
acyl, alkoxy or alkoxy carbonyl having in each case up
to 6 carbon atoms, nitro, cyano, halogen, phenyl or
straight-chain or branched alkyl having up to 6 carbon
atoms, which in its turn can be substituted by hydroxyl,
amino, carboxyl, straight-chain or branched acyl,
alkoxy or alkoxy carbonyl having in each case up to 5
carbon atoms,

and/or are optionally substituted by a group of the
formula —S(O)_{c3}NR⁵⁰R⁵¹, wherein c3, R⁵⁰ and R⁵¹
have the abovementioned meaning of c3, R⁵⁰ and R⁵¹
and are identical to or different from these,

A³ represents a 5- to 6-membered aromatic or saturated
heterocyclic ring having up to 3 heteroatoms from the
series consisting of S, N and/or O or phenyl, which are
optionally substituted up to 3 times in an identical or
different manner by amino, mercaptyl, hydroxyl,
formyl, carboxyl, straight-chain or branched acyl,
alkylthio, alkoxyacetyl, alkoxy or alkoxy carbonyl
having in each case up to 6 carbon atoms, nitro, cyano,

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164

trifluoromethyl, azido, halogen, phenyl or straight-
chain or branched alkyl having up to 6 carbon atoms,
which in its turn can be substituted by hydroxyl,
carboxyl, straight-chain or branched acyl, alkoxy or
alkoxy carbonyl having in each case up to 5 carbon
atoms,

and/or is substituted by a group of the formula
—CO_{d3}—NR⁵³R⁵⁴, wherein

d3 denotes the number 0 or 1,

R⁵³ and R⁵⁴ are identical or different and denote
hydrogen, phenyl, benzyl or straight-chain or
branched alkyl or acyl having in each case up to 5
carbon atoms,

or an isomer or salt thereof.

2. A compound according to claim 1 of formula (III-I), in
which

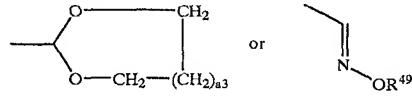
R⁴² represents pyranyl or morpholinyl, which are option-
ally substituted up to twice in an identical or different
manner by formyl, trifluoromethyl, phenyl, carboxyl,
hydroxyl, straight-chain or branched acyl, alkoxy or
alkoxy carbonyl having in each case up to 5 carbon
atoms, nitro, cyano, azido, fluorine, chlorine, bromine,
phenyl or straight-chain or branched alkyl having up to
5 carbon atoms, which in its turn can be substituted by
hydroxyl, halogen, trifluoromethyl, amino, carboxyl,
straight-chain or branched acyl, alkoxy, alkoxy carbonyl
or acylamino having in each case up to 4 carbon
atoms, or by a radical of the formula —OR⁴⁵, wherein

R⁴⁵ denotes straight-chain or branched acyl having up
to 4 carbon atoms or a group of the formula

—SiR⁴⁶R⁴⁷R⁴⁸, wherein

R⁴⁶, R⁴⁷ and R⁴⁸ are identical or different and denote
straight-chain or branched alkyl having up to 4
carbon atoms,

and/or are substituted by a radical of the formula



wherein

a3 denotes the number 0, 1, 2 or 3,
R⁴⁹ denotes hydrogen or straight-chain or branched
alkyl having up to 3 carbon atoms,

R⁴³ and R⁴⁴, including the double bond, form a furyl,
thienyl or phenyl ring, which are optionally substituted
up to 3 times in an identical or different manner by
formyl, carboxyl, hydroxyl, amino, straight-chain or
branched acyl, alkoxy or alkoxy carbonyl having in
each case up to 5 carbon atoms, nitro, cyano, azido,
fluorine, chlorine, bromine, phenyl or straight-chain or
branched alkyl having up to 5 carbon atoms, which in
its turn can be substituted by hydroxyl, amino,
carboxyl, straight-chain or branched acyl, alkoxy or
alkoxy carbonyl having in each case up to 4 carbon
atoms,

A³ represents tetrahydropyranyl, tetrahydrofuranyl,
thienyl, pyrimidyl, phenyl, morpholinyl, pyrimidyl,
pyridazinyl or pyridyl, which are optionally substituted
up to twice in an identical or different manner by
hydroxyl, formyl, carboxyl, straight-chain or branched
acyl, alkythio, alkoxyacetyl, alkoxy or alkoxy carbonyl
having in each case up to 4 carbon atoms, fluorine,
chlorine, bromine, nitro, cyano, trifluoromethyl or
straight-chain or branched alkyl having up to 4 carbon

atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having, in each case up to 4 carbon atoms,

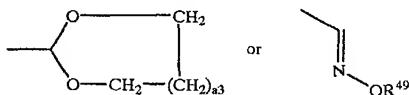
and/or are substituted by a group of the formula $-(CO)_{d3}-NR^{53}R^{54}$, wherein
d3 denotes the number 0 or 1,
R⁵³ and R⁵⁴ are identical or different and denote
hydrogen, phenyl, benzyl or straight-chain or
branched alkyl or acyl having in each case up to 4
carbon atoms,

or an isomer or salt thereof.

3. A compound according to claim 1 of the formula (III-I),
in which

R⁴² represents imidazolyl, oxazolyl, oxadiazolyl or
thiazolyl, which are optionally substituted up to twice
in an identical or different manner by formyl,
trifluoromethyl, phenyl, straight-chain or branched
acyl, alkoxy or alkoxycarbonyl having in each case up
to 4 carbon atoms or straight-chain or branched alkyl
having up to 4 carbon atoms, which in its turn can be
substituted by hydroxyl, fluorine, chlorine,
trifluoromethyl, carboxyl, amino, straight-chain or
branched acyl, alkoxy, alkoxycarbonyl or acylamino
having in each case up to 3 carbon atoms or by the
radical of the formula $-O-CO-CH_3$,

and/or are substituted by a radical of the formula



wherein

a3 denotes the number 0, 1 or 2,
R⁴⁹ denotes hydrogen or methyl,

R⁴³ and R⁴⁴, including the double bond, form a furyl,
thienyl or phenyl ring, which are optionally substituted
up to twice in an identical or different manner by
formyl, carboxyl, hydroxyl, amino, straight-chain or
branched acyl, alkoxy or alkoxycarbonyl having in
each case up to 4 carbon atoms, nitro, cyano, fluorine,
chlorine, phenyl or straight-chain or branched alkyl
having up to 3 carbon atoms, which in its turn can be
substituted by hydroxyl, amino, carboxyl, straight-
chain or branched acyl, alkoxy or alkoxycarbonyl hav-
ing in each case up to 3 carbon atoms,

A³ represents tetrahydropyranyl, phenyl, thienyl, pyrim-
idyl or pyridyl, which are optionally substituted up to
twice in an identical or different manner by formyl,
carboxyl, straight-chain or branched acyl, alkylthio,
alkyloxyacyl, alkoxy or alkoxycarbonyl having in each
case up to 3 carbon atoms, fluorine, chlorine, bromine,
nitro, cyano, trifluoromethyl, or straight-chain or
branched alkyl having up to 3 carbon atoms, which in
its turn can be substituted by hydroxyl, carboxyl,
straight-chain or branched acyl, alkoxy or alkoxycar-
bonyl having in each case up to 3 carbon atoms,

and/or are substituted by a group of the formula
 $-(CO)_{d3}-NR^{53}R^{54}$, wherein

d3 denotes the number 0 or 1,

R⁵³ and R⁵⁴ are identical or different and denote
hydrogen or straight-chain or branched alkyl or acyl
having in each case up to 3 carbon atoms,
or an isomer or salt thereof.

4. A compound according to claim 1 of the formula (III-I)
in which

R⁴² represents imidazolyl, oxazolyl, thiazolyl or
oxadiazolyl, which are optionally substituted up to
twice in an identical or different manner by
ethoxycarbonyl, phenyl or by methyl or ethyl, wherein
the alkyl radicals in their turn can be substituted by
hydroxyl, chlorine, ethoxycarbonyl, oxycarbonylm-
ethyl or methoxy,

R⁴³ and R⁴⁴ together, including the double bond, repre-
sent phenyl, which is optionally substituted by nitro,

A³ represents phenyl or phenyl which is substituted by
fluorine, or pyrimidyl

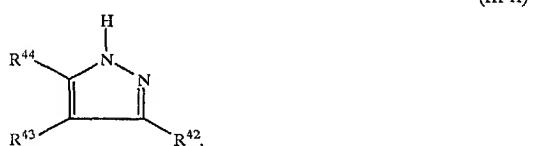
or an isomer or salt thereof.

5. A pharmaceutical composition comprising at least one
compound of the formula (III-I) according to claim 1.

6. A pharmaceutical composition comprising a combina-
tion of at least one compound of the formula (III-I) accord-
ing to claim 1 and at least one organic nitrate or an NO
donor.

7. A pharmaceutical composition comprising a combina-
tion of at least one compound of the formula (III-I) accord-
ing to claim 1 and compounds which inhibit the breakdown
of cyclic guanosine monophosphate (cGMP).

8. Process for the preparation of a compound according to
claim 1 of the formula (III-I), comprising
[A3] reacting a compound of the formula (III-I)

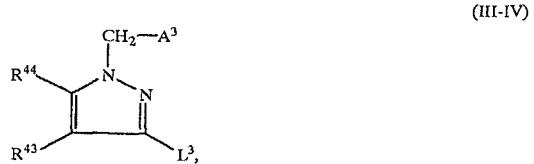


in which
R⁴², R⁴³ and R⁴⁴ have the meaning in claim 1,
with a compound of the formula (III-III)



in which
A³ has the meaning in claim 1, and
D³ represents triflate or halogen,
in an inert solvent, optionally in the presence of a base,
or

[B3] reacting a compound of the formula (III-IV)



in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning and
L³ represents a radical of the formula
 $-SnR^{55}R^{56}R^{57}ZnR^{58}$, iodine, bromine or triflate,
wherein
R⁵⁵, R⁵⁶ and R⁵⁷ are identical or different and denote
straight-chain or branched alkyl having up to 4
carbon atoms and

167

R^{58} denotes halogen,
with a compound of the formula (III-IV)

 $R^{42}-T^3$

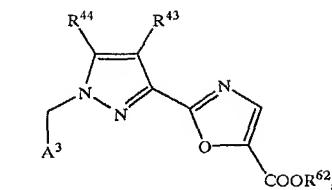
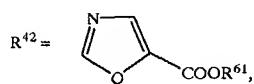
(III-V),

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in which

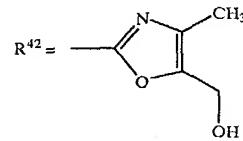
R^{42} has the abovementioned meaning and
in the case where $L^3=SnR^{55}R^{56}R^{57}$ or ZnR^{58} ,
 T^3 represents triflate or represents halogen, and
in the case where L^3 -iodine, bromine or triflate,
 T^3 represents a radical of the formula $SnR^{55}R^{56}R^{57}$,
 ZnR^{58} or $BR^{59}R^{60}$, wherein
 R^{55} , $R^{56}R^{57}$ and R^{58} have the abovementioned
meaning of R^{55} , R^{56} , R^{57} and R^{58} and are identical
to or different from these, and
 R^{59} and R^{60} are identical or different and denote
hydroxyl, aryloxy having 6 to 10 carbon atoms or
straight-chain or branched alkyl or alkoxy having
in each case up to 5 carbon atoms, or together
form a 5- or 6-membered carbocyclic ring,

in a palladium-catalysed reaction in an inert solvent, or
[C3] in the case where



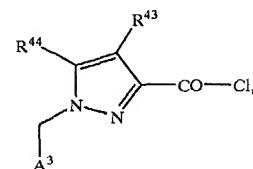
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in which
 A^3 , R^{43} , R^{44} and R^{62} have the abovementioned
meaning, or

[D3] in the case where $R^{42}=$ 

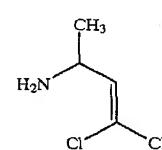
reacting a compound of the formula (III-VIII)

(III-VIII)



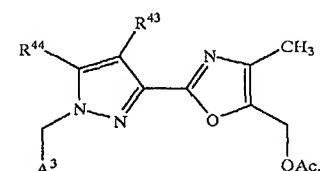
in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning,
with the compound of the formula (III-IX)

(III-IX)



in the system $NaOCO-CH_3/N$ -methylpyrrolidine
to give the compound of the formula (III-Ib)

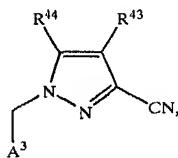
(III-Ib)



in which
reacting a compound of the formula (III-VI)

(III-VI),

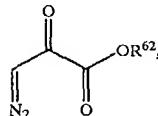
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in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning,
with a diazo compound of the formula (III-VII)

(III-VII)

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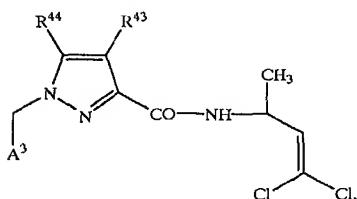


in which
 R^{62} represents straight-chain or branched alkyd having
up to 4 carbon atoms,
in the presence of a copper salt or rhodium salt to give a
compound of the formula (III-1a)

in which
 R^{43} , R^{44} and A^3 have the abovementioned meaning,
and the acetyl group is then split off by the action of
potassium hydroxide in methanol, or

169

by reacting the compound of the formula (III-VIII) with the compound of the formula (III-IX), to give a compound of the formula (III-X)



in which

R⁴³, R⁴⁴ and A³ have the abovementioned meaning, and preparing the hydroxymethyl compound in a further step by reacting with potassium hydroxide, and optionally converting said hydroxymethyl compound into the corresponding alkoxy compound by alkylating said hydroxymethyl compound, or

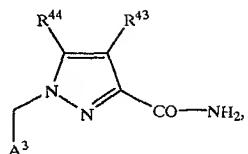
[E3] reacting a compound of the formula (III-XI)

(III-X) 5
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[F3] reacting a compound of the formula (III-XIV)

170

(III-XIV)



in which

A³, R⁴³ and R⁴⁴ have the abovementioned meaning, with a compound of the formula (III-XV),

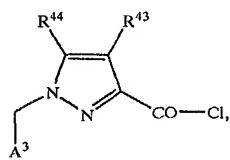
Br—CH₂—CO—R⁶³

(III-XV),

in which

R⁶³ denotes straight-chain or branched alkyl or alkoxy-carbonyl having in each case up to 4 carbon atoms, in an inert solvent to give the compound of the formula (III-Ic)

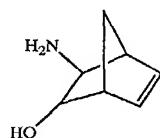
(III-XI)



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in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning, with the compound of the formula (III-XII)

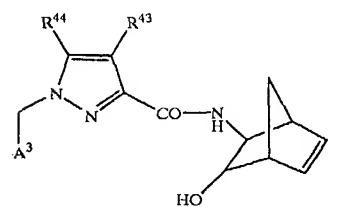
(III-XII) 40
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to give the compound of the formula (III-XIII)

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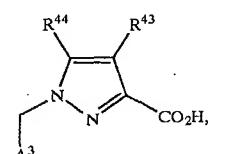
(III-XIII)



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reacting a carboxylic acid of the formula (III-XVI)

(III-XVI)



in which

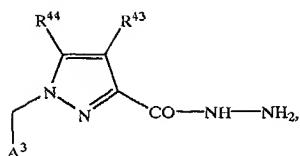
A³, R⁴³ and R⁴⁴ have the abovementioned meaning, with hydrazine hydrate to give the compound of the formula (III-XVII)

in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning, and then reacting said compound of formula (III-XIII) in a retro-Diels-Alder reaction, or

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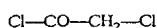
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(III-XVII)



in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning,

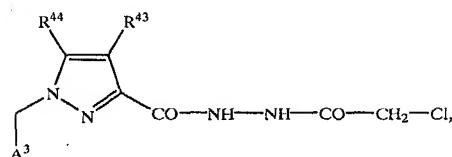
and reacting said compound of the formula (III-XVII) ¹⁵
 with the compound of the formula (III-XVIII)



(III-XVIII)

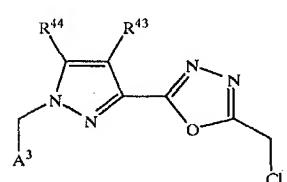
to give the compound of the formula (III-XIX) ²⁰

III-XIX)



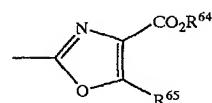
in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning, ³⁵

and then, cyclizing the compound of the formula (III-XIX) by reacting with phosphorus oxytrichloride to
 give the compounds of the formula (III-Id) ⁴⁰



in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning, or ⁵⁰

[H3] in the case where R^{42} represents a radical of the formula ⁵⁵



wherein

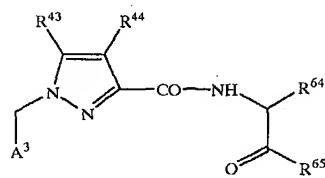
R^{64} denotes hydrogen or straight-chain or branched
 alkyl having up to 4 carbon atoms and ⁶⁵

172

R^{65} has the scope of meaning of the secondary sub-
 stituents listed above under the heterocyclic radical
 R^{42} ,

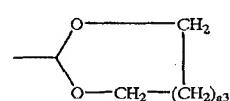
5 reacting a compound of the formula (III-XX) ¹⁵

(III-XX)



in which
 A^3 , R^{43} , R^{44} , R^{64} and R^{65} have the abovementioned
 meaning,
 with PPh_3/I_2 optionally in the presence of a base, or

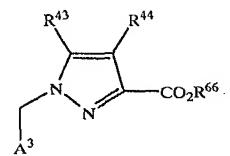
[13] in the case where R^{42} represents the group of the
 formula ²⁰



wherein $a3$ denotes the number 0, 1, 2, or 3, ²⁵

reducing a compound of the formula (III-XXI) ³⁰

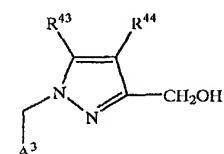
(III-XXI)



in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning and
 R^{66} has the abovementioned meaning of R^{64} and is
 identical to or different from this, ³⁵

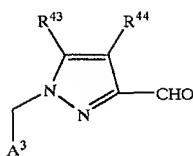
by customary methods to give a compound of the formula
 (III-XXII) ⁴⁰

(III-XXII)



in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning, ⁴⁵

and then oxidizing the compound of the formula (III-
 XXII) to give the compound of the formula (III-XXIII) ⁵⁰



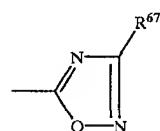
(III-XXIII)

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in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning, or
 by directly converting the compound of the formula (III-XXI) 15 into the compound of the formula (III-XXIII),

and, finally reacting the compound of the formula (III-XXIII) with 1,2- or 1,3-dihydroxy by conventional 20 methods, or

[J3] in the case where R^{42} represents the radical of the 25 formula

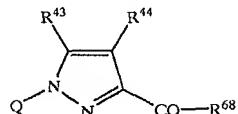


(III-XXIV)

30

wherein
 R^{67} has the abovementioned meaning of R^{65} and is 35 identical to or different from this,

reacting a compound of the formula (III-XXIV)

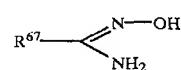


(III-XXV)

50

in which
 R^{43} and R^{44} have the abovementioned meaning and
 Q represents hydrogen or represents the $-\text{CH}_2-\text{A}^3$ radical and
 R^{68} represents halogen or straight-chain or branched
 alkoxy having up to 4 carbon atoms, preferably 55 chlorine, methoxy or ethoxy,

with a compound of the formula (III-XXV)



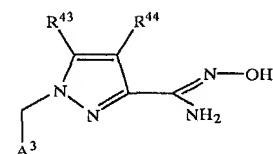
60

R^{67} has the abovementioned meaning,

optionally in the presence of a base, and, in the case where $Q=\text{H}$, the product is then reacted with, a compound of the general formula $\text{A}^3-\text{CH}_2-\text{Br}$ (III-XXVI), in which A has the abovementioned meaning, or

reacting a compound of the formula (III-XXVII)

(III-XXVII)



in which
 A^3 , R^{43} and R^{44} have the abovementioned meaning

with a compound of the formula (III-XXVIII)

 $R^{67}-\text{CO}-\text{R}^{68}$

(III-XXVIII)

35

in which
 R^{67} has the abovementioned meaning of R^{67} and is identical to or different from this and
 R^{68} has the abovementioned meaning of R^{68} and is identical to or different from this optionally in the presence of a base.

9. The process according to claim 8, which is for the preparation of a compound of formula (III-I) which contains a radical $-\text{S}(\text{O})_{c3}\text{NR}^{50}\text{R}^{51}$ or $-\text{S}(\text{O})_{c3}\text{NR}^{50}\text{R}^{51}$, said process further comprising reacting an unsubstituted compound of formula (III-I) with thionyl chloride to produce an intermediate product, and thereafter reacting said intermediate product with $\text{HNR}^{31}\text{R}^{32}$ or $\text{HNR}^{31}\text{R}^{32}$.

10. The process according to claim 8, which further comprises introducing or varying R^{42} , R^{43} , R^{44} and/or A^3 by reduction, oxidation, splitting off of protective groups and/or nucleophilic substitution.

11. The process according to claim 8, wherein, in [H3] D^3 represents bromine or wherein in [B3] T^3 represents bromine.

12. The process according to claim 8, wherein [H3] said base is triethylamine.

13. Method for the treatment of cardiovascular diseases, said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (III-I) according to claim 1.

14. Method for preventing or treating the consequences of a cerebral infarction event said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (III-I) according to claim 1.

15. The method according to claim 13, wherein the cerebral infarction event is an apoplexia cerebri selected from the group consisting of apoplexy, cerebral ischaemias and crania-cerebral trauma.